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Tiotropium bromide in asthma patients: an alternative to inhaled long-acting beta-agonists?

M Lane
Respiratory Registrar, Queen Elizabeth Hospital, Gateshead, Tyne and Wear, UK

TITLE Tiotropium bromide step-up therapy for adults with uncontrolled asthma

AUTHORS Peters SP, Kunselman SJ, Icitovitch N et al.

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Correspondence to M Lane, Respiratory Department, Queen Elizabeth Hospital, Sheriff Hill, Gateshead NE9 6BR, UK

tel. +44 (0)7950 963177
e-mail matthew.lane@nuth.nhs.uk

SUMMARY

Asthma affects an estimated 5.4 million people in the UK.[1] Many patients remain symptomatic despite regular inhaled therapies. Given the burden of asthma and the heterogeneity of patients, the role of new therapeutic options requires evaluation. Tiotropium bromide has a well-established role in the management of chronic obstructive pulmonary disease (COPD). This is the first comprehensive study to evaluate its use in asthma.

The study recruited 210 adult patients with suboptimal asthma control despite British Thoracic Society (BTS) step 2 therapies (beclomethasone 80 µg, twice daily).

The triple-blind, placebo-controlled, three-way crossover design compared 14-week periods of step-up treatment of a long-acting anti-muscarinic (tiotropium 18 µg, once daily) versus a long-acting beta-agonist (salmeterol 50 µg, twice daily) versus increased inhaled glucocorticoids (beclomethasone 160 µg, twice daily).

The primary outcome measure was the morning peak expiratory flow rate (PEFR). Secondary outcome measures included forced expiratory volume in one second (FEV_1) (pre- and post-bronchodilator using the short-acting beta-agonist albuterol), asthma control days, rescue bronchodilator use, exacerbations and validated asthma questionnaires.

Tiotropium was shown to be superior to increased inhaled glucocorticoid with respect to the primary outcome measure (mean difference of 25.8 l/min, $p<0.001$) and most secondary outcome measures, including the proportion of asthma-control days and the score on the Asthma Control Questionnaire. Tiotropium was also shown to be non-inferior to salmeterol for all assessed outcome measures and superior with regard to the bronchodilator response to albuterol (FEV_1 mean difference of 0.071, $p<0.001$).

The authors conclude that tiotropium, when added to a regular inhaled glucocorticoid in patients with poorly controlled asthma, has an efficacy equivalent to salmeterol in improving lung function and symptoms.

OPINION

In adults with asthma who remain symptomatic despite low-dose inhaled glucocorticoid, options for step-up therapy include the addition of an inhaled long-acting beta-agonist (LABA) and increasing the dose of inhaled glucocorticoid.[2] Additional options in selected patients include a trial of a leukotriene modifier and theophylline.[2] Short-acting anti-muscarinics have been available for the treatment of bronchospasm for years. It is surprising that the role of long-acting anti-muscarinics (LAMA) in asthma has not been comprehensively evaluated before now.

While the study's primary outcome variable will be criticised, its secondary outcome variables are mostly patient-centred. A genuine clinically applicable evaluation of exacerbation rates was not possible given the short duration of the study.

The finding that tiotropium resulted in a greater improvement in PEFR and symptom control compared with doubling the dose of inhaled glucocorticoid is not surprising. Inhaled glucocorticoids have a relatively flat dose-response curve, such that doubling the dose is unlikely to result in significant clinical improvements.[3]

The most interesting finding of the study was that tiotropium was not inferior to salmeterol as step-up therapy. Recent concerns about infrequent but life-threatening exacerbations associated with LABA use makes tiotropium an attractive alternative.[4]

A potential role for LAMA therapy in asthma lies in those patients who remain symptomatic despite a combination of inhaled glucocorticoid and LABA therapy (BTS stages 3–4). Peters and colleagues perhaps nod to this with the observation that the FEV_1 did not increase following administration of a short-acting beta-agonist in patients taking a LABA but did in those taking LAMA. This role is currently being investigated (ClinicalTrials.

gov number NCT00772538) in a study evaluating tiotropium in addition to usual care in patients with severe persistent asthma. Some clinicians are already using tiotropium in this context.

Although concerns have also been raised about a possible association between tiotropium and cardiovascular events in patients with COPD, this has not been borne out in larger studies.[5–6] Further trials are required to determine the long-term efficacy and safety of tiotropium as an asthma therapy.

It will not be long before clinical trials of glucocorticoid-LAMA combination inhalers are under way; perhaps in the near future 'triple-therapy' (glucocorticoid-LABA-LAMA) combination inhalers will be available for the treatment of asthma.

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